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technical advantages and is ethically compelling as it allows for non-destructive sampling. As indicated for blood MT, the adaptation of analytical methods for use with blood can require some care because of the dilute nature of blood. Otherwise, there is no reason that blood chemistry parameters for fish and other wildlife cannot be as well characterized as a diagnostic tool as it is for humans. While the behavior and relevance of some contaminants in fish blood are well understood, generally it can be said that contaminants in blood are under-utilized. In large part this is because of the traditional use of destructive sampling and the analysis of organs such as liver and kidney.

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Is the Body Residue a Useful Dose Metric for Assessing Toxicity?

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Clearly the toxicity of a compound depends its concentration at the receptor site and the duration of site occupation. Aquatic toxicology made use of the concept that the dose at the receptor was proportional to the concentration in the organism which was in turn found to be proportional to the exposure concentration with aqueous exposures. The use of external exposure media as the dose metric was severely challenged by the presence of multiple routes of exposure and factors that alter contaminant bioavailability, e.g. sediment exposures. The suggestion that body residue would serve as a useful dose metric was advocated by McCarty (1986) with the Critical Body Residue (CBR) concept linked to the concentration to cause 50% mortality in a population for non-polar, non-metabolized toxicants (McCarty 1990). In a recent review article (Barron et al. 2002), the utility of the CBR approach in assessing toxicant effects in aquatic biota was questioned. The main thrust of this review was to highlight the large variability observed among species and toxicants when tissue concentrations are used as the dose metric. As Barron et al. (2002) aptly point out, "CBRs" have been promoted as consistent across different chemicals, species, and exposure conditions. We agree with some of the points made in their review, especially those concerning the high variability observed for some "modes of action"; however, we feel that some the observed variability was overstated and several important factors that affect the association between tissue residue and biological response were overlooked. To be fair, we feel that the following points are crucial for determining the utility of using body residue as a dose metric and if not considered, lead to high variability when making comparisons.

The term CBR by itself lacks a coherent definition. CBR can mean many things to various researchers, such as the lethal residue associated with a 50% mortality (LR_{50}), the residue associated with the some percentage sublethal response (e.g., ER_{25}), or the threshold residue associated with any adverse effect. Obviously, for an accurate comparison among "CBRs" the response metric has to be standardized. Several terms have been used for expressing body residue as the dose metric, including CBR, Lethal Body Burden (LBB), Internal Lethal Concentration (ILC), and Lethal Residue (LR), all with different definitions and derivations. To make accurate comparisons, terminology that clearly defines the population level response and the proportion of the population responding is required, e.g., 96-h LR_{50}. Standardization of terminology is critical to ensure that comparisons are made on an equivalent basis.

Time is a critical variable in characterizing a response metric (e.g., LR_{50}). Recent research has shown that the tissue concentrations associated with using body residue as a response metric can decrease over time (e.g., Chaisuksant et al. 1997). This is not surprising, for even McCarty and Mackay (1993), in their description of the utility of the body residue approach, gave different residue concentrations for acute and chronic exposures. Thus, comparisons between tests must be done on an equivalent exposure duration. When compounds act by specific mechanisms of action, the integrated exposure may be as critical as the body residue observed (Verhaar et al. 1999). Finally, another temporal consideration is that different modes of toxic action caused by a toxicant may be expressed with differing durations of exposure. For example, acute mortality may result after a few days

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due to one mode of action such as narcosis, but additional organisms may die weeks later due to another mode of action, such as a weakened immune system.

Lipid normalization is likely necessary to compare responses on a body residue basis among species for many hydrophobic toxicants. When the mechanism of action is non-polar narcosis, the site of action is the lipid membrane. Under these conditions the storage lipids can shunt material from the site of toxic action, thus organisms with higher lipid content will require a higher body residue to show toxicity. In these cases, normalizing for the amount of lipid will account for this extra storage. Even in cases where the toxicity is by a specific mode of action, if storage lipid can sequester contaminant away from the site of toxic action, lipid normalization will improve comparisons between studies. Likewise, if the toxicant is not highly lipid soluble, then normalization will not be useful.

For those compounds that exert their toxicity through a specific receptor, it is generally recognized that different species will respond at quite different doses of a particular toxicant depending on the specific characteristics of the receptor and toxicant. When specific receptors are involved in the toxic response, substantial differences between species are expected. This is well known in mammalian toxicology and should be expected for aquatic toxicology as well. The potential mechanism of action can be better assessed for the organism if body residues are used since the complications from bioavailability and multiple routes of exposure are eliminated. This approach also allows comparison of the sensitivity between species and allows selection of the most sensitive organisms for protection.

Accurate classification of the mode of action is crucial. Some compounds may exhibit different modes of action for different species. This is likely for any compound that acts by a specific mode of toxic action. Changes in the receptor or the absence of a specific receptor in a species could cause the specific acting compound to behave more like a narcotic (anesthetic). For some toxicants our knowledge of the mechanism of toxicity is lacking. Additionally, some toxicants may exhibit several modes of action, necessitating a more rigorous classification system.

Metabolism must be considered (Barron et al. 2002). In many cases, the extent of biotransformation of contaminants has not been examined. Further, the role of metabolites in the toxicity of compounds is usually not known. Organophosphates are one exception because the oxon metabolite is clearly the toxic form. Appropriate use of the body residue approach will allow for exclusion or inclusion of metabolites as contributing toxicants.

Assessing toxicity based on tissue residues for elements will likely be difficult, especially for those that are essential and highly regulated by species. It is well known from past studies that species exhibit a large range in ability to regulate internal metal concentrations. The body residue approach may be useful for some elements and species; however, large variability is expected.

Additional stressors are expected to affect the observed toxicity whether the dose metric is on a body residue or external concentration basis. For example, variable salinity, temperature, pH, and oxygen content not only affect the amount bioaccumulated, which is accounted for when using body residue as the dose metric, but may also affect the physiology and sensitivity of the organisms, producing variable results. However, by expressing the toxicity on a body residue basis, bioavailability issues can be separated from physiological impacts on the toxic response. These variables must be considered to avoid confounding factors.

In general, Barron et al. (2002) have alerted us to many factors that need to be considered when using body residues as a dose metric. However, some of their examples were selective and potentially misleading. It was not clear that many of the important issues addressed above were considered when making comparisons among studies, particularly ensuring that the measurement was to the same endpoint, e.g., the LR_{50}. Further, in many cases only a range of values was given and not the more appropriate mean and standard error. It is important to note whether the range is driven by a few outliers or whether the data are just scattered. We also noticed that for some examples, wet and dry weights were included and used to highlight variability. Obviously, all tissue concentrations must be expressed in comparable units.

It should also be recognized that there are limited datasets available for rigorous scientific evaluation of the body residue approach. This concept has only recently received widespread interest (McCarty 1986; McCarty and Mackay 1993) and researchers have not had sufficient time to collect high-quality data for this new paradigm. Good examples that support the body residue approach do exist in the literature.

Bottom line: We believe that the use of body residue as a dose metric can be very useful for predicting toxicity responses. When additional research is completed, keeping in mind many of the points outlined above, the body residue approach will provide an accurate dose metric for assessing and predicting biological responses. The approach will provide a foundation for the assessment of bioaccumulation data that hereto could not be well assessed in terms of stress to the organisms. Granted, new research will provide both new approaches and clarify the limits for the use of body residues as a dose metric. The variability obtained with environmental dose metrics, such as water and sediment concentrations, is one big step removed from the concentrations inside the organism that are associated with the receptor. Because in many cases the internal concentration is based on whole-body measurements, we still are just estimating the amount that actually interacts with the receptor leading to the biological response, but we are one step closer to the receptor and the bioavailability issues are removed. All things being equal, body residues should help improve risk assessment and improve

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our understanding of the factors that determine the toxicity of contaminants to aquatic organisms.

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